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Additive Analgesic Effects of Oxycodone and Ibuprofen in the Oral Surgery Model

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Purpose: A traditional approach to achieve greater analgesic efficacy is to combine an efficacious dose of a nonopioid with a dose of an opioid sufficient to produce additive analgesia without a substantial increase in the incidence of adverse effects. This study evaluated the additive analagesic effects of the combination of ibuprofen and oxycodone.

Patients and Methods: A dose of 400 mg ibuprofen was compared with 400 mg ibuprofen with oxycodone in doses of 2.5, 5, or 10 mg in the oral surgery model of acute pain. Analgesic efficacy was measured with category and visual analog scales at 15, 30, 45, and 60 minutes and hourly up to 6 hours.

Results: Ibuprofen plus 10 mg oxycodone produced significantly greater analgesia compared with the other three groups, as measured by the visual analog scale from 15 minutes after drug administration up to the 2-hour observation. All four treatments were similar from 3 to 6 hours, with the area under the pain intensity difference curve being similar across groups. Neither the 2.5-mg nor the 5-mg oxycodone dose provided any additive analgesia over ibuprofen at any points. Addition of oxycodone resulted in a dose-related increase in the number of patients reporting adverse effects, with significantly greater drowsiness and vomiting at the 10-mg dose.

Conclusions: These results indicate that additive analgesia can be achieved for the combination of a nonsteroidal anti-inflammatory drug and an orally effective opioid, with faster onset of relief for the combination of 400 mg ibuprofen and 10 mg oxycodone over the first 2 hours after administration, but at the expense of an increased incidence of adverse events.

Despite the well-documented efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) and the inflammatory origin of dental pain, some patients do not receive adequate relief from a normal therapeutic dose of an NSAID. Because of the relatively flat dose-response relationship for NSAIDS, increasing the dose beyond the maximum recommended will produce a marginal increase in analgesic activity but with an increased incidence of adverse effects. Switching to a combination such as acetaminophen plus codeine usually results in less analgesia and produces more side effects than when an NSAID is included. Analgesic adjuvants other than opioids (caffeine, barbiturates, or phenothiazines) have been removed from most drug combinations because of lack of additive analgesia activity at the doses used or concern for safety (phenacetin). These limitations of currently available analgesics and combinations result in a therapeutic dilemma of balancing less than optimal analgesia against increased side effect liability and concern for safety with chronic administration.

The traditional approach to overcoming these well-recognized limitations is to combine a therapeutic dose of a nonopioid, to achieve the maximal possible analgesia through one mechanism of action, with the minimal dose of an opioid that provides additive analgesia but without an unacceptable increase in the incidence of adverse effects. This forms the basis for classic analgesic combinations such as acetaminophen or aspirin plus codeine or oxycodone. An obvious combination based on this concept is to combine a therapeutic dose of an NSAID such as 400 mg ibuprofen with a dose of an opioid that produces additive analgesia, but with an acceptable incidence of adverse effects. However, the ability to demonstrate an additive effect for an opioid in combination with an NSAID has proved difficult. Codeine in doses of 20 to 60 mg has been evaluated in combination with varying doses of ibuprofen. Results using 200 mg ibuprofen plus 15 mg codeine were indistinguishable from ibuprofen 200 mg over the course of 5 hours postoperatively.[1] Similarly, the addition of 20 mg codeine to a sustained-release formulation of 300 mg ibuprofen did not result in any additive effects, but did produce a greater incidence of side effects.[2] Comparison of 400 mg ibuprofen plus 60 mg codeine to ibuprofen 400 mg

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also failed to show analgesia for the initial dose but tended to provide greater analgesia over the next 3 days, with only a modest increase in side effects.[3] The results of these and other studies[4-7] provide equivocal evidence for the additive effects of codeine in the range of 20 to 60 mg when administered in combination with ibuprofen 400 mg. As is usually seen for therapeutic doses of codeine in ambulatory patients, this additive analgesic effect is accompanied by an increased incidence of side effects such as drowsiness, dizziness, nausea, and vomiting.

Analgesic combinations containing oxycodone are generally perceived as more efficacious than codeine-containing combinations. This appears logical given the 10- to 12-fold greater potency attributed to oxycodone in comparison with codeine,[8,9] and administration of the recommended oxycodone dose in these combinations (5 mg every 6 hours) should result in analgesia equivalent to the usual 60 mg dose of codeine in analgesic combinations. The therapeutic advantage to oxycodone combinations is the ability to administer two tablets, a dose of 10 mg oxycodone, to produce greater analgesia.[10] The current study combined 400 mg ibuprofen with varying doses of oxycodone to determine whether an additive effect of an opioid could be demonstrated in combination with a normal therapeutic dose of an NSAID. The results suggest that while additive analgesia can be achieved at the highest dose of oxycodone evaluated, the side effect liability is substantial, and use of this combination should be reserved for clinical situations where the additional analgesia is required.

Patients and Methods

Subjects were oral surgery outpatients undergoing the surgical removal of two to four impacted third molars with midazolam sedation and local anesthesia using 2% lidocaine with 1:100,000 epinephrine. A mucoperiosteal flap was raised and retracted, bone was removed, and the teeth sectioned as needed to facilitate extraction. Sutures were used to close the surgical flap, a gauze was placed over each extraction site, and patients were moved to the recovery room for observation and postoperative data collection. Potential subjects were excluded if they had a history of an allergic or adverse reaction to any medication, a history of drug abuse or dependence, and if they had taken an analgesic, anti-inflammatory, or central nervous system depressant drug (with the exception of the midazolam used for the procedure) within 48 hours before oral surgery. Female patients of childbearing potential and not using an effective method of contraception also were excluded.

After surgery, subjects were questioned every 15 minutes regarding the loss of mandibular anesthesia and the onset of pain using category scales. At the report of "moderate" pain consistent with the offset of anesthesia, subjects completed a 100-mm visual analog scale for pain intensity and were then randomly allocated to one of the four treatments: ibuprofen 400 mg, ibuprofen 400 mg plus 2.5 mg oxycodone, ibuprofen 400 mg plus 5 mg oxycodone, or ibuprofen 400 mg plus 10 mg oxycodone.

Subjects completed questionnaires for pain intensity and pain relief at 15, 30, 45, 60 minutes, and hourly up to 6 hours after drug administration. Pain intensity was rated with a category scale as none (0), mild (1), moderate (2), or severe (3) and with a 100-mm visual analog scale (VAS) with a left endpoint of "none" and a right endpoint of "worse possible pain." These data were used to derive a pain intensity difference score at each time point by subtracting the starting pain value from each of the pain intensity ratings at each subsequent observation. Pain relief was rated with a five-point category scale as no pain relief (0), a little pain relief (1), some pain relief (2), a lot of relief (3), or complete relief (4) and with a VAS with a left endpoint of "no relief" and a right endpoint of "complete relief."

Data were analyzed with the BMDP Statistical Software Package (SPSS, Inc, Chicago, IL). Statistical differences between treatments for VAS data were determined by repeated measures analysis of variance over the first 2 hours after administration as a measure of early analgesic activity and for the entire 6-hour observation period. The source and magnitude of differences between treatments at each time were determined by one-way analysis of variance with post hoc comparisons by Duncan's multiple range test. Categorical data were compared with the Kruskal-Wallis test. For all statistical tests, differences in P values $< .05$ in a two-tailed test were considered significant. A sample size of 30 subjects per group was calculated based on a previous study using the oral surgery model.[11]

Results

The study sample consisted of 118 usable subjects equally distributed among the four drug groups (Table 1). The mean age was characteristic of the young adult population normally undergoing the removal of impacted third molars and did not differ substantially between groups in gender distribution, height, weight, doses of adjunctive drugs administered, or difficulty of the surgical procedures. The mean starting pain as measured by category scale (2.2 to 2.4) and VAS (61.8 to 67.3) were very similar between groups. The similarity of the prognostic factors for postoperative

Table 1. SUMMARY OF DEMOGRAPHIC CHARACTERISTICS FOR BOTH STUDIES

	N	Age	Gender	Height (cm)	Weight (kg)	Midazolam (mg)	Lidocaine (mg)	Surgical Difficulty*
Ibuprofen 400	29	21.6 ± 3.7	18 F 11 M	170.7 ± 10.2	64.3 ± 9.7	4.8 ± 0.6	186.6 ± 44.6	11.3 ± 3.9
Ibuprofen 400 mg Oxycodone 2.5 mg	29	21.5 ± 5.6	11 F 18 M	175.5 ± 10.9	69.9 ± 11.6	4.8 ± 0.8	189.0 ± 30.1	12.6 ± 3.0
Ibuprofen 400 mg Oxycodone 5 mg	29	20.8 ± 5.4	18 F 11 M	169.4 ± 10.4	65.4 ± 14.5	4.6 ± 0.8	185.6 ± 34.0	13.1 ± 2.5
Ibuprofen 400 mg Oxycodone 10 mg	31	22.1 ± 6.2	21 F 10 M	167.4 ± 7.9	63.7 ± 10.3	4.9 ± 1.1	197.8 ± 49.6	12.7 ± 3.2

*Surgical difficulty classified as simple extraction (1), soft tissue impaction (2), partial bony impaction (3), or full bony impaction (4); value is sum for all teeth extracted.

pain (difficulty of the surgical procedure and starting pain) and the demographic characteristics of the groups indicated that these factors did not likely confound the outcome of the study.

Analgesic effect, as measured by the VAS pain intensity difference, showed significantly greater effect for the combination of ibuprofen plus 10 mg oxycodone at 15, 30, 45, and 60 minutes and at 2 hour after drug administration in comparison to ibuprofen 400 mg alone (Fig 1, upper panel). Analgesic effect reached a peak between 2 and 4 hours, followed by a gradual decrease over the last 2 hours of the observation period. None of the treatments could be separated from each other at any of the observation periods from 3 to 6 hours. The sum of the pain intensity difference scores over the first 2 hours during analgesic onset was significantly greater for the oxycodone 10 mg plus ibuprofen 400 mg than for the ibuprofen 400 mg alone (Fig 1, lower panel) but did not differ between treatments for the sum of the 6 hours. Similar, but nonsignificant, trends were seen between treatments for the pain intensity difference scores as measured by category scale (data not shown).

The pain relief VAS showed similar trends for greater relief from the combination of ibuprofen plus 10 mg oxycodone at the early time points, but no difference between treatments over the last 2 to 6 hours (Table 2), or for the sum of the pain relief scores for the entire observation period. Pain relief measured by category scale showed greater, but nonsignificant, mean scores for the combination of ibuprofen plus 10 mg oxycodone at each observation from 30 minutes to 2 hours, but did not differ at later points (Table 2).

The incidence of adverse effects was low in the ibuprofen 400 mg group and were not significantly increased by the addition of 2.5 mg or 5 mg oxycodone (Table 3). The addition of 10 mg oxycodone resulted in a significant increase in the incidence of drowsiness ($P < .001$) and vomiting ($P < .05$), while decreasing the number of subjects who did not report any side effects to 5 of the 31 who received this dose.

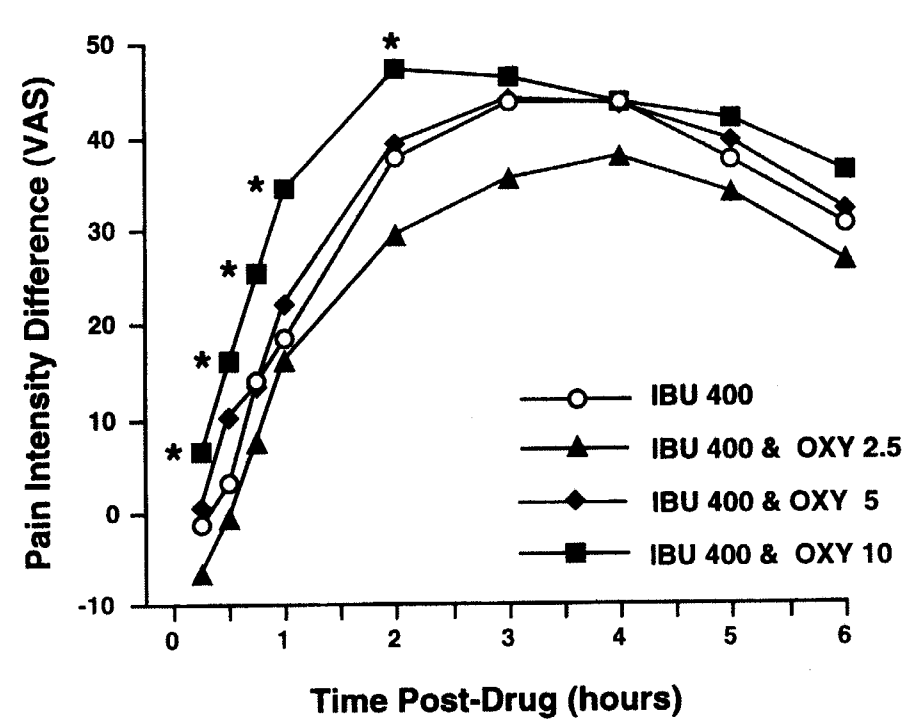

FIGURE 1. Analgesic onset over time derived from the difference in pain intensity from baseline as measured by visual analog scale (upper panel). Sum of the pain intensity difference scores for the first 2 hours during analgesic onset (left bar) and for the entire 6-hour observation period (right bar) for each of the four treatment groups (lower panel).

Table 2. PAIN RELIEF AS MEASURED BY VISUAL ANALOG SCALE (VAS) AND CATEGORY SCALE

	Time Post-Surgery (min)								
	15	30	45	60	120	180	240	300	360
Pain relief (VAS)									
Ibuprofen 400	11.9 ± 14.7	23.1 ± 25.8	40.5 ± 32.8	43.9 ± 32.0	68.6 ± 28.6	72.6 ± 31.5	75.5 ± 33.3	70.8 ± 35.1	61.1 ± 42.1
Ibuprofen 400 Oxycodone 2.5	9.7 ± 14.7	18.6 ± 20.8	28.4 ± 29.0	35.4 ± 29.7	60.7 ± 29.0	67.0 ± 31.5	70.3 ± 30.3	65.7 ± 36.7	59.2 ± 37.5
Ibuprofen 400 Oxycodone 5	13.3 ± 21.3	27.2 ± 28.0	35.0 ± 30.4	42.7 ± 34.5	64.9 ± 33.0	69.8 ± 35.3	71.2 ± 34.1	66.5 ± 35.1	62.1 ± 35.3
Ibuprofen 400 Oxycodone 10	16.4 ± 22.5	34.4 ± 32.7*	44.8 ± 33.2	53.8 ± 32.8*	71.6 ± 28.9	71.7 ± 31.1	68.0 ± 35.1	65.0 ± 36.6	60.3 ± 40.6
Pain Relief (Category)									
Ibuprofen 400	0.6 ± 0.7	1.0 ± 1.0	1.7 ± 1.2	1.7 ± 1.2	2.6 ± 1.2	2.7 ± 1.3	2.9 ± 1.3	2.6 ± 1.4	2.2 ± 1.5
Ibuprofen 400 Oxycodone 2.5	0.5 ± 0.6	0.8 ± 0.8	1.3 ± 1.1	1.7 ± 1.0	2.4 ± 1.0	2.6 ± 1.2	2.7 ± 1.1	2.4 ± 1.4	2.3 ± 1.4
Ibuprofen 400 Oxycodone 5	0.7 ± 0.9	1.2 ± 1.1	1.6 ± 1.2	1.9 ± 1.2	2.5 ± 1.2	2.6 ± 1.3	2.6 ± 1.3	2.5 ± 1.3	2.3 ± 1.3
Ibuprofen 400 Oxycodone 10	0.7 ± 0.9	1.4 ± 1.2	1.9 ± 1.2	2.2 ± 1.2	2.8 ± 1.1	2.7 ± 1.2	2.6 ± 1.3	2.5 ± 1.4	2.3 ± 1.5

*$P < .05$ vs IBU 400.

Discussion

The current study attempted to determine a dose of an orally effective opioid that produced an optimal additive effect by evaluating a range of opioid doses that would be predicted to span from a subtherapeutic dose (2.5 mg), including the dose normally used in combination with a nonopioid (5 mg), and a dose producing greater analgesia (10 mg). Consistent with this hypothesis, the combination of ibuprofen 400 mg plus oxycodone 2.5 mg did not result in any additive analgesic effects. However, the combination of ibuprofen with 5 mg oxycodone also did not result in any detectable additive effects on any of the four analgesic scales used at any point. The 10-mg oxycodone dose produced additive analgesic effects, but only at the early points when the onset of racemic ibuprofen was still increasing. This advantage was not detectable at any times from 3 to 6 hours, with all four groups resulting in similar overall area under the analgesic time response curve. These data suggest that the only advantage to adding an opioid to an NSAID in the oral surgery model is at times when the onset of analgesic activity of the NSAID component of the combination is suboptimal, presumably because the delay inherent in the conversion of the relatively inactive R(−)-isomer of ibuprofen to the active S(+)-isomer.[12]

This additive effect of the 10-mg dose is at the expense of a high incidence of central nervous system-mediated adverse effects. Only 16% of subjects in this group did not report side effects, in comparison to 62% of symptom-free subjects in the ibuprofen 400-mg group. Although it is likely that some of the side effects experienced over the first few hours postsurgically were related to residual effects of the midazolam sedation and central effects of local anesthetic absorption, these data suggest an approximate twofold increase in side effects due to the opioid. Yet, the overall analgesic effect over the 6-hour observation period was negligible and confined to the initial 2 hours postdrug administration. This relationship between transient, marginal additive analgesia at the expense of a substantial increase in side effect liability suggests a questionable therapeutic benefit.

An alternative to the delayed onset of analgesia in the oral surgery model is the well-documented effect of preventive analgesia. Administration of an NSAID such as ibuprofen[13] or flurbiprofen[14] before the offset of local anesthesia significantly attentuates the onset

Table 3. INCIDENCE OF ADVERSE EFFECTS REPORTED

	Drowsiness	Nausea	Vomited	Dizzy	Other	None
Ibuprofen 400	3	2	0	0	5	18/29
Ibuprofen 400 Oxycodone 2.5	6	2	2	1	5	17/29
Ibuprofen 400 Oxycodone 5	8	5	0	1	2	14/29
Ibuprofen 400 Oxycodone 10	20†	6	5*	5	6	5/31†

*$P < .05$.
†$P < .001$.

of pain in the oral surgery model, but without any appreciable increase in side effects in comparison with administering the same drug after pain onset. Additional benefit can be achieved by using a long-acting local anesthetic, such as etidocaine or bupivacaine, in combination with the NSAID pretreatment.[15] Although not commercially available in the United States, administration of the S-isomer of ibuprofen results in a faster onset and greater peak analgesia than administration of the same-milligrams dose of racemic ibuprofen.[12] No detectable increase in side effect incidence is associated with this therapeutic benefit, and the duration of drug action is comparable, indicating a favorable benefit-to-risk relationship.

Comparisons of analgesic activity in the oral surgery model is based on statistical analysis of grouped data from samples usually ranging from 20 to 50 per treatment. Although appropriate for clinical trials, this approach fails to account for the large variability that exists between patients in their response to the surgical procedure, the analgesic effects of the drug, and sensitivity to side effects. Virtually all studies using oral medications use fixed doses so that the actual dose (in mg/kg) varies according to body weight. Pharmacokinetic and pharmacogenetic differences also contribute to variability in analgesic responsiveness,[16] especially in the conversion of codeine to morphine-3-glucuronide, the presumed active metabolite of codeine.[17] These considerations make it unlikely that the analgesic effects for specific drugs and doses, especially when given in combination, can be generalized across the population of all patients. It is possible, based on the results of well-controlled trials, that an optimal dose of an NSAID might still be inadequate in a specific patient, whereas addition of an opioid resulting in a significant elevation in side effects for a group of subjects would be well tolerated by an individual patient.

The availability of oxycodone as a single-entity generic formulation permits optimization of the additive effects of an NSAID-opioid combination for each patient after an outpatient surgical procedure. The optimal dose of an NSAID can be administered to a patient before pain onset to block the effects of prostaglandin E_2 released in the postoperative period[18] due to the expression of cyclooxygenase-2. This dose should be continued on a "by-the-clock" basis, based on the recommended dosing interval for the drug, to avoid pain associated with the offset of analgesic activity and the delayed onset associated with the absorption, distribution, and pharmacolgic effects of subsequent doses. For pain that is unrelieved by this strategy, the minimal effective dose of oxycodone that results in an additive analgesic effect could be administered on an "as needed" basis for a minimal number of doses and adjusted between one and two 5-mg tablets to balance the additive analgesic effects against the likelihood of side effects. For some patients, a few doses of 5 mg oxycodone in combination with the NSAID should provide adequate analgesia and minimal side effects, while others may require 10 mg doses. At the very least, subjects who experience drowsiness may accept this as a reasonable alternative to inadequate pain relief. By administering the opioid selectively to patients who are experiencing suboptimal analgesia from an NSAID, only those patients receiving the therapeutic benefit are exposed to the potential risk of increased adverse effects. Conversely, administering a fixed-dose combination to all subjects would likely result in a spectrum of effects ranging from unnecessary adverse effects without therapeutic benefit, some patients having an optimal balance, and some patients having little additive analgesia but substantial side effects.

The availability of a fixed-dose combination of ibuprofen and an orally effective analgesic, hydrocodone, suggests the ability to achieve the additive effects of the NSAID-opioid combination without the need to individualize the opioid dose or deal with the regulatory issues associated with prescribing controlled substances. This formulation combines 200 mg ibuprofen with 7.5 mg hydrocodone, a dose that is approximately equivalent to a 45-mg dose of codeine.[19] As reviewed elsewhere,[20] administration of a single dose of this formulation results in a suboptimal dose of ibuprofen, equivalent to a single tablet of an over-the-counter formulation, with a near maximal dose of the opioid. Increasing the dose to two tablets will provide the normal therapeutic ibuprofen dose but with a dose of hydrocodone likely to produce a high incidence of adverse effects. Extrapolating from the results of the current study and the few published studies on the analgesic effectiveness of hydrocodone in the oral surgery model suggests that one tablet of the ibuprofen-hydrocodone combination should be combined with a 200- to 400-mg dose of ibuprofen to result in the maximal beneficial effects of the NSAID with an additive opioid effect. However, no published studies have evaluated this combination in the oral surgery model.

The results of this study show an additive effect for the most widely used NSAID when administered in combination with an orally effective opioid, in therapeutic doses of each agent, to patients without contraindications to either drug. Given the need to provide greater analgesia to some patients after surgical procedures, the combination of an NSAID and an opioid appears to provide a therapeutic alternative if preventive strategies have not proved effective or were not appropriate to the therapeutic environment. Optimization of the benefit-to-risk ratio associated with the combination can be best achieved by only administer-

ing the opioid to patients who need the additional analgesic benefit and titrating the dose on the basis of side effects.

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